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Biodegradable microcontainers as an oral drug delivery system for poorly soluble drugs

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Purpose: To fabricate microcontainers in biodegradable polylactic acid (PLLA) polymer films using hot embossing, and investigate the application of the fabricated microcontainers as an oral drug delivery system for a poorly soluble drug.

Introduction: One of the key challenges in oral drug delivery is to increase the solubility and dissolution of poorly water soluble drugs and thereby, improve the oral bioavailability of the drug. One solution is to modify the actual drug formulation, but recently micro fabricated drug delivery devices have been proposed as an alternative method for delivering drugs orally [1],[2]. Microcontainers are small polymeric devices consisting of a flat base with a walled reservoir and have been suggested as a potential approach to improve the oral bioavailability of drugs [3],[4]. The microcontainers vary from traditional spherical micro- and nanoparticles as only one side of the microcontainers is open which allows for unidirectional release of the drug directly to the intestinal mucosa. The cavity of the microcontainers is filled with drug and subsequently coated with a lid of a pH-sensitive polymer to protect the drug from degradation and premature release in the stomach. The polymer-lid will then be dissolved at the higher pH in the small intestine and the drug is released and absorbed through the intestinal wall (Fig 1). A challenge that has not been addressed so far is to fabricate the microcontainers using a biodegradable polymer. PLLA was chosen as the biodegradable polymer for fabrication of the microcontainers. The polymer is approved by the US Food and Drug administration (FDA) for drug delivery purposes and categorised as a biopolymer with long biodegradation time and therefore, suitable to use for fabrication of the microcontainers for oral drug delivery [5].

Results: For fabrication of the PLLA microcontainers, a film of PLLA was deposited by spin coating on a silicon wafer. The film was heated above the polymer glass transition temperature (T_g), and a Ni stamp was forced into the film (Fig 2A) [6]. Following cooling of the film the stamp was removed, exposing the formed microcontainers with an inner diameter of 220 μm and a height of 100 μm (Fig 2B). The PLLA microcontainers were filled with amorphous furosemide sodium salt (produced by spray drying) using a simplified version of a screen printing technique (Fig 3). A gastric-resistant lid of Eudragit L100 (soluble above pH 6) was subsequently spray coated onto the cavity of the microcontainers (Fig 3). The release of the drug from the microcontainers was carried out in biorelevant gastric medium (pH 1.6), followed by release in a biorelevant intestinal medium (pH 6.5) using a μ -Diss profiler and also a flow through set-up in conjunction with UV imaging. From both release experiments it was observed that the Eudragit layer prevented drug release in biorelevant gastric medium, while an immediate release of the amorphous furosemide salt was seen in the biorelevant intestinal medium (Fig 4). Future work includes the investigation of drug release of individual containers.

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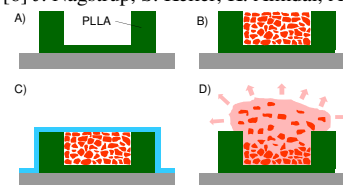


Figure 1. Illustration of the experimental methods. A) Fabrication of PLLA microcontainers. B) Filling with amorphous furosemide salt. C) Spray coating of a lid of Eudragit L100. D) Dissolution of coating and release of drug.

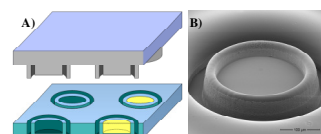


Figure 2. A) Graphics illustrating the hot embossing process after the stamp is released from the polymer film. B) SEM image of one PLLA microcontainer.

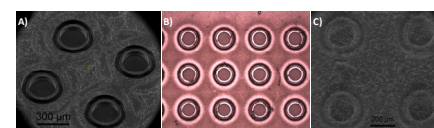


Figure 3. SEM images of PLLA microcontainers. A) Empty microcontainers. B) Microcontainers filled with amorphous furosemide salt. C) Microcontainers filled with amorphous furosemide salt and spray coated with Eudragit L100.

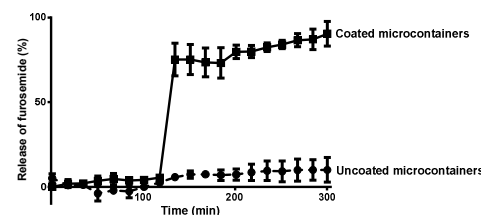


Figure 4. Release profiles obtained from PLLA microcontainers filled with amorphous furosemide salt and with and without Eudragit L100 coating in pH 1.6 (from 0-120 min) and pH 6.5 (120-300 min).